Combined impact of negative lifestyle factors on cardiovascular risk in children: a randomized prospective study

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Abstract: PURPOSE: Negative lifestyle factors are known to be associated with increased cardiovascular risk (CVR) in children, but research on their combined impact on a general population of children is sparse. Therefore, we aimed to quantify the combined impact of easily assessable negative lifestyle factors on the CVR scores of randomly selected children after 4 years. METHODS: Of the 540 randomly selected 6- to 13-year-old children, 502 children participated in a baseline health assessment, and 64% were assessed again after 4 years. Measures included anthropometry, fasting blood samples, and a health assessment questionnaire. Participants scored one point for each negative lifestyle factor at baseline: overweight; physical inactivity; high media consumption; little outdoor time; skipping breakfast; and having a parent who has ever smoked, is inactive, or overweight. A CVR score at follow-up was constructed by averaging sex- and age-related z-scores of waist circumference, blood pressure, glucose, inverted high-density lipoprotein, and triglycerides. RESULTS: The age-, sex-, pubertal stage-, and social class-adjusted probabilities (95% confidence interval) for being in the highest CVR score tertile at follow-up for children who had at most one (n = 48), two (n = 64), three (n = 56), four (n = 41), or five or more (n = 14) risky lifestyle factors were 15.4% (8.9-25.3), 24.3% (17.4-32.8), 36.0% (28.6-44.2), 49.8% (38.6-61.0), and 63.5% (47.2-77.2), respectively. CONCLUSIONS: Even in childhood, an accumulation of negative lifestyle factors is associated with higher CVR scores after 4 years. These negative lifestyle factors are easy to assess in clinical practice and allow early detection and prevention of CVR in childhood.

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List of abbreviations
CVR – cardiovascular risk; BMI – body mass index; PA – physical activity; MVPA – moderate-and-vigorous physical activity.

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Abstract (max. 350 words)

Purpose Negative lifestyle factors are known to be associated with increased cardiovascular risk (CVR) in children, but research on their combined impact on a general population of children is sparse. Therefore, we aimed to quantify the combined impact of easily assessable negative lifestyle factors on the CVR scores of randomly selected children four years later. **Methods** 502/540 randomly selected 6- to 13-year-old children participated in a baseline health assessment and 64% were assessed again four years later. Measures included anthropometry, fasting blood samples and a health-assessment questionnaire. Participants scored one point for each negative lifestyle factor at baseline: overweight, physically inactivity, high media consumption, little outdoor time, skipping breakfast, and having a parent who has ever smoked, is inactive or overweight. A CVR score at follow-up was constructed by averaging sex- and age-related z-scores of waist circumference, blood pressure, glucose, inverted high density lipoprotein and triglycerides. **Results** The age-, sex-, pubertal stage and social class-adjusted probabilities (95% CI) for being in the highest CVR score tertile at follow-up for children who had at most one (n=48), two (n=64), three (n=56), four (n=41) or five and more (n=14) risky lifestyle factors were 15.4 (8.9 to 25.3)%, 24.3 (17.4 to 32.8)%, 36.0 (28.6 to 44.2)%, 49.8 (38.6 to 61.0)%, and 63.5 (47.2 to 77.2)%, respectively. **Conclusions** Even in childhood, an accumulation of negative lifestyle factors is associated higher CVR scores four years later. These negative lifestyle factors are easy to assess in clinical practice and allow early detection and prevention of CVR in childhood.

Key words: behavior, longitudinal, metabolic syndrome, physical activity, overweight, media consumption, breakfast, parents

Implications and Contribution:

Any single negative lifestyle factor may lead to increased cardiovascular risk, but research on their combined impact is sparse. This study shows that children with 3 or more risk factors had more than a 3-times higher risk of having an elevated cardiovascular risk profile in adolescence when compared to children with one or no unhealthy lifestyle factors.

Introduction

The reasons for increased cardiovascular risk (CVR) in children are multifactorial. In addition to genetic predisposition, intrauterine factors, the early postpartal period, cultural, socioeconomic and environmental variables, modifiable lifestyle parameters and their consequences also play an important role.[1-3] Lifestyle modifications at a young age might be a promising strategy to prevent cardiovascular disease. In clinical practice, early identification of at-risk children by simple means such as easily assessable negative lifestyle factors is a crucial and relevant step of prevention.

Several single negative lifestyle factors associated with increased CVR in children are known. These include child-related factors such as overweight,[4] low physical activity (PA),[3] high media consumption and sedentary behavior,[5, 6] omission of breakfast,[7] and little time spent outdoors.[8] Parental factors such as physical inactivity,[9] smoking[9] and overweight also contribute.[10] Because these individual factors are not independent of each other and often appear in combination,[11] it is important to know their combined impact on CVR. This has been shown in a prospective study in adults in which the relative risk of cardiovascular disease mortality increased with a decreasing number of positive lifestyle factors such as healthy eating, a physically active lifestyle, low alcohol consumption and the absence of smoking.[12] As there is no comparable study in children, we aimed to quantify the combined

impact of easily accessible negative lifestyle factors in randomly selected healthy children on their CVR score four years later.

Methods

Participants

The study was approved by the ethics committees of the University of Basel and the Swiss Federal Institute of Technology Zurich, as well as by the Cantonal Ethical Committee of Aargau, Switzerland.

We analysed data from the Kinder-Sportstudie (KISS) study, a cluster-randomized controlled trial investigating the effects of a physical activity (PA) intervention on PA, CVR and obesity in schoolchildren. A detailed study design has been published.[13, 14] In summary, we randomly selected 28 of 190 consenting classes from 15 schools of two of the 26 provinces of Switzerland after stratification by neighborhood type (urban vs. rural), grade (first and fifth grade) and migrant prevalence representative for the Swiss population (i.e., 10 – 30%). For the present analysis, data from the baseline assessment in August 2005 and follow-up assessment four years later (2009) were used (Figure 1). Informed consent for all measurements was provided by each child and a parent.

Measurements

Children's anthropometry and CVR

All measures were taken in schools as described earlier.[13]. Standing height was measured by a wall-mounted stadiometer and body weight was determined with an electronic scale (Seca, Basel, Switzerland). Body mass index (BMI; kg/m^2) was calculated and *z*-scores were derived according to World Health Organization reference data with overweight defined as a BMI *z*-score above one standard deviation.[15] Waist circumference was measured by a

flexible tape midway between the lowest rib and the iliac crest. Blood pressure was assessed at the right arm five times after a resting period of 5 minutes with an automated oscillograph (Oscillomate, CASMedical Systems, Branford, CT, USA). The mean of the three closest measurements were *z*-transformed based on published age- and sex-specific norm values.[16] Blood samples were drawn in the morning after an overnight fasting for measurement of glucose, high density lipoprotein cholesterol and triglycerides. Serum glucose was measured by the hexokinase method, high density lipoprotein cholesterol and triglycerides with a homogenous enzymatic colorimetric test. Within assay and between assay CV were 0.7% and 1.6% for HDL, 1.5% and 1.8% for triglycerides, respectively. We then computed a composite CVR score by averaging the *z*-scores of all components of the metabolic syndrome (waist circumference, blood pressure (mean of systolic and diastolic blood pressure *z*-score), glucose, inverted high density lipoprotein cholesterol, and triglycerides).[17] Skewed data of high density lipoprotein cholesterol and triglycerides were log-transformed. The remaining normally distributed variables were z-transformed using grade- and sex-specific means and standard deviations derived from the baseline and follow-up sample, respectively. Parents were asked to rate children's pubertal stage by a questionnaire with a simple explanation and line drawings of Tanner stages.[18] Pubertal stage at baseline was defined as prepubertal (Tanner stage 1) and pubertal (Tanner stage >1) based on breast development for girls and pubic hair for boys.

Negative lifestyle factors

Children's negative lifestyle factors at baseline were assessed by questionnaires completed by their parents. Although we have not tested reliability, internal consistency and validity of our lifestyle questions, Crohnbach alphas for subscales assessing eating and physical activity habits of children by their parents with comparable designs ranged from 0.4 to 0.8 and ICCs for test-retest reliabilities from 0.5 to 0.9.[19, 20] Questions included information about

parental body height and weight, smoking habits ("Do you currently smoke?" – yes/no. "Are you a former smoker?" – yes/no), and their participation in PA ("On average, how much time each day do you spend in PA in which you are out of breath and sweating?" – below 30 min, about 30 min, 1 h. 2 h, 3h or more). Child-level questions inquired about time spent outdoors ("On a normal day, how much time does your child spend outdoors?" – below 30 min, 30-60 min, 1-2 h, 2-4 h, 4-6 h, or >6h), breakfast consumption ("In a normal week, on how many days does your child skip breakfast?" – 5-7 d/wk, 2-4 d/wk, 0-1 d/wk), and media consumption ("On a normal day, how many hours does your child spend in front of a screen?" – time in minutes). PA was objectively assessed by accelerometry (GT1M, Actigraph, Shalimar, FL, USA) continuously worn around the hip for 7 days. The sampling time was set to one minute. Periods with over 15 min of continuous zero values were considered as non-wearing time and were omitted before analyses. PA data were included if at least three weekdays and one weekend day of measurements with a minimum of 12 h for weekdays and 10 h for weekend days were recorded. Time per day spent in moderate-and-vigorous PA (MVPA) was obtained by counting the minutes above 2000 counts min^{-1}.[21] We transformed all these lifestyle factors in dichotomous variables with 1 denoting "risk" and 0 denoting "no risk". Definitions and cut-points are given in Table 1. Where possible, these cut-points were derived from previous studies. Children's overweight was based on a BMI *z*-score above one standard deviation.[15] A cut-point of 90 min/d of MVPA was taken from a study indicating MVPA levels below 90 min/d are associated with increased CVR in children.[22]. The threshold of 120 min/d of media consumption was based on the American Academy of Pediatrics' recommendation [23] and previous studies which recommend limiting children's screen time to less than two hours per day.[24, 25] Although there are neither clear guidelines nor cut-points for the amount of time a child should spend outdoors, 120 min/d as a threshold has been previously used in this context. [8, 26] Skipping breakfast was defined as having

breakfast less than nearly every day (i.e. less than 5 times per week). This cutoff had been shown to be associated with obesity in a large cohort of children and adolescents of similar age.[27] For parental lifestyle factors, one point was given for each of the following: at least one parent was overweight with a BMI above 25 kg/m^2, physically inactive (i.e., reported less than 30 min/d of PA that induced sweating [28]) and a current or previous smoker (to include potential risk of smoking during pregnancy and exposure to secondhand smoke).[29, 30]

Statistical analyses

Children with information on at least three of the eight baseline lifestyle factors and with CVR follow-up data were included in the analysis. Based on a most conservative approach, missing information was not imputed, as only 8 children reported <6 lifestyle factors. Sensitivity analyses excluding these children did not change the results. Thus, children with information on only three lifestyle factors could have had a minimum of three, and a maximum of eight, negative lifestyle risk factors. Baseline comparisons between participating and non-participating children were calculated using a multilevel linear or logistic regression model with class as random effect, adjusted for sex, grade and group (intervention versus control group as the study was designed as a randomized-controlled trial). Baseline characteristics are given as unadjusted means and standard deviations, unless stated otherwise. A high CVR score was defined as the highest tertile of the age-and sex-related composite CVR score. To quantify the combined impact of negative lifestyle factors on the CVR four years later, we counted the number of negative lifestyle factors for each child and then used a multilevel logistic regression model with the dichotomized CVR (highest tertile vs. others) at follow-up as outcome and the number of negative lifestyle factors (0 or 1 as reference, versus 2, 3, 4, or 5 or more factors) as predictor, adjusting for sex, grade, group allocation, pubertal stage, parental education level (low versus middle and high) and with class as random effect. Adjusted probabilities were then calculated from the obtained odds ratios. Additionally, we

adjusted the model for the baseline CVR score. Analyses were performed using Stata version 11.0 and the level of significance was set at 0.05.

Results

Participation

Figure 1 provides a flow chart of the study. Of the 540 children invited to participate in 2005, 502 (93%) agreed to participate.[14] Of those, 480 answered the baseline questionnaires assessing lifestyle factors. CVR parameters were obtained in 71% of the 312 children who participated in the follow-up measurements. Only 8 children reported 3-5 lifestyle factors whereas all others reported 6 to 8 lifestyle factors. Participating children did not differ from non-participating children in age, height, weight, BMI, and baseline CVR. However, compared to non-participating children, participating children were less likely to have parents in the low education group (5% vs. 14%; $p<0.01$), to have parents who were overweight (53% vs. 64%; $p<0.05$), to be in the high media consumption group (29% vs. 42%; $p<0.05$) or to skip breakfast (7% vs. 14%; $p<0.05$). Characteristics of participating children are given in Table 2. Compared to children in the middle or lowest tertile of the CVR score, children in the highest tertile had an unfavorable BMI (21.0 (2.9) vs. 17.9 (2.6) kg/m^2; $p<0.001$), a higher waist circumference (70.2 (7.5) vs. 61.7 (5.9) mm; $p<0.001$), a higher blood glucose level (5.0 (0.5) vs. 4.6 (0.4) mmol/l; $p<0.001$), a higher triglycerides level (1.0 (0.4) vs. 0.7 (0.3) mmol/l; $p<0.001$), a lower high-density lipoprotein level (1.3 (0.3) vs. 1.6 (0.3) mmol/l; $p<0.001$), and a higher mean blood pressure (91.1 (8.1) vs. 85.9 (8.3) mmHg; $p<0.001$).

Individual impact of negative lifestyle factors on CVR

Of all negative lifestyle factors, only being overweight at baseline was associated with a significantly higher probability of having a high CVR *at baseline* [probability = 89.2 (95%

confidence interval: 81.5 to 94.0)%; p<0.001)]. Children who were overweight, or whose parents were overweight or smoked, were significantly more likely to have a high CVR *at follow up* four years later than their counterparts (Table 3). These associations remained significant even after adjustment for baseline CVR.

Combined impact of negative lifestyle factors on CVR

Figure 2 shows the adjusted probabilities (and their 95% confidence interval) of being in the upper tertile of the CVR score as a function of the number of negative lifestyle factors. Forty-eight (22%) children had at most one negative lifestyle factor, whereas 64 (29%), 56 (25%), 41 (18%), and 14 (6%) had two, three, four, and five or more negative lifestyle factors, respectively. Probabilities of having a high CVR increased with increasing number of negative lifestyle factors and ranged from 15.4 (95% CI 8.9 to 25.3)% for one or no negative lifestyle factors to 63.5 (47.2 to 77.2)% for five or more negative lifestyle factors. Even after additional adjustment for the baseline CVR score (subsample n=198), probabilities for being in the upper tertile of the CVR score remained significantly higher with probabilities of 31.3 (22.7 to 41.4)% (p=0.041) for three, 43.0 (30.1 to 56.9)% (p=0.026) for four, and 55.4 (36.0 to 73.4)% (p=0.016) for five or more negative lifestyle factors compared to children with at most one negative lifestyle factor.

Discussion

This study examined the combined impact of easily assessable negative lifestyle factors in randomly selected children on their CVR four years later. The number of negative lifestyle factors in children at baseline was positively associated with an unfavorable CVR score four years later, independent of CVR score at baseline. Children with three, four, or five or more negative lifestyle factors at baseline had a 36%, 50% and 64% chance, respectively, of being

in the highest CVR tertile four years later, compared to a 15% chance for children with one or no negative lifestyle factors.

The lifestyle factors considered in this study are known to be related to CVR in children.[3-5, 7-10] Obesity is an obvious key player in the risk profile as it is clearly linked to increased CVR, including metabolic syndrome in adolescence[4] and coronary heart disease in adulthood.[31] Skipping breakfast has been shown to be related to higher BMI in childhood,[7, 27] but also to increased waist circumference, blood lipids and BMI in adulthood if skipping breakfast is maintained.[7] PA and sedentary behavior are independently associated with cardiovascular health[3]. Less than 90 minutes of MVPA per day has been shown to be associated with clustering of CVR factors[22] and an increase in MVPA has led to a better CVR profile,[2, 14] supporting causality. Especially in younger children, time spent outdoors is a determinant of PA[8, 32] and obesity.[8] Increased screen time is associated with overweight,[33, 34] but also with subclinical markers of cardiovascular disease such as retinal microvasculature,[5] clustered metabolic risk,[6] and adult obesity.[24]

In addition to individual lifestyle factors of the child, parental lifestyle factors play an essential role in predicting CVR in children.[9, 10] Parental BMI is a strong predictor of children's BMI[35, 36] and can also predict metabolic syndrome in adolescence.[10] Passive exposure to cigarette smoke during childhood is associated with higher blood pressure[37] and endothelial dysfunctions[38, 39] which seem to persist into adulthood.[39] Moreover, parental PA influences the child's PA behavior[40, 41] and consequently, the child's CVR.

In our study, only children's and parental overweight and parental smoking status were significant individual predictors of high CVR assessed four years later. The absence of other significant associations may be due to a lack of power, considering that only 46% of children

with baseline lifestyle data had CVR data at follow-up. Moreover, the thresholds used for the definition of "negative" had an influence on exposure prevalence and therefore on the effect. As prevalence rates of negative lifestyle factors ranged between 7% and 62% (Table 2), it is possible that the exposure variable did not properly differentiate between groups. Nevertheless, the major aim of the current study was to quantify the combined impact of these negative lifestyle factors as children do not show true metabolic syndrome but rather "a tendency towards cardiometabolic disease." Although rarely considered, negative lifestyle factors tend to cluster and are not independent of each other. Clustering of cardiovascular disease risk factors, which imparts an even greater risk than the sum of the individual risk factors in adults, also takes place in childhood and tracks into adolescence, as shown in this study. For instance, it could be shown that unhealthy diet, fitness, smoking, and excessive alcohol consumption were related to each other among adults[11] and that the presence of these factors was related to cardiovascular disease mortality.[12] Moreover, skipping breakfast seems to co-occur with other unhealthy lifestyle habits such as smoking and physical inactivity.[42] With this study, we could show that the clustering of negative lifestyle factors predicting CVR in adults also exists in children.

There are several strengths inherent to our study, including a relatively large, representative sample of Swiss children of both genders, across a broad age range, a battery of lifestyle factors which can be easily assessed by a simple questionnaire in clinical practice, a composite CVR score including the five key metabolic syndrome variables and a longitudinal design. Limitations include the use of internal z-scores for some CVR factors for which no official norms exist and the substantial drop-out rate at follow-up which may hamper generalizability. The use of questionnaires filled out by parents and children may induce recall bias by the child and reporting biases towards social desirability which may have led to an underestimation of risk factors. This, however, was most likely balanced among CVR

tertile groups. Although participants and non-participants were comparable regarding their baseline anthropometric characteristics and CVR, we cannot completely rule out the presence of some selection bias as differences for parental education and overweight, media consumption, and breakfast consumption existed, questioning generalizability of our findings. Nonetheless, one would expect a higher drop out among unhealthier participants during the follow-up leading to an under-, rather than over-, estimation of the longitudinal associations reported here. We assumed that each of these lifestyle factors affects cardiovascular health equally. Weighting them according to their individual burden on cardiovascular pathways may have been more appropriate. However, this was not possible due to the lack of established knowledge of the individual burdens on cardiovascular pathways in children. Dichotomizing lifestyle factors facilitates their use in clinical practice, however, health lifestyle parameters are often continuous and therefore, the use of a cut-off leads to a loss of more detailed information. Additionally, most of the lifestyle factors were self-reported in order to be easily assessable. There might, therefore, be a reporting bias. Assuming that individuals generally report their state and behaviors better than they are in reality, the real effects of these lifestyle factors on children's CVR are expected to be even higher than reported here. Yet, the reporting bias is expected to be balanced among CVR groups.

Conclusions

The early identification of children with a high risk for developing an unfavourable cardiovascular risk profile by simple means such as easy assessable negative lifestyle factors is a crucial and relevant step of prevention. Notably, an unfavorable CVR profile in childhood may be the first sign for cardiovascular disease later in life as a cluster of CVR factors in children such as high blood pressure, blood lipids and BMI, is related to the presence[43] or

markers[44] of early atherosclerosis. Physicians could fill out a simple checklist of relevant lifestyle factors within a few minutes in order to estimate a child's risk for developing an unfavorable CVR some years later. Importantly, the impact of these negative lifestyle factors on the CVR four years later was independent of baseline CVR. This suggests that a clustering of unhealthy lifestyle factors in 6- to 13-year-old children can result in an unfavorable CVR score within only four years. This would allow early, individually-targeted prevention efforts to protect children from developing true cardiovascular risk factors, which ultimately lead to cardiovascular disease.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

UM supervised the data collection, analyzed and interpreted the data; and drafted the article. CS helped with statistical analyses, interpretation of the data and critically revised the article. TB was involved in data acquisition and critically revised the article. ES was involved in data acquisition and critically revised the article. LZ was involved in the conception and design of the study and critically revised the article. JP was involved in the conception and design of the study and critically revised the article. SK was involved in the conception and design of the study, interpretation of the data, provided overall supervision, and was involved with drafting the manuscript. All authors read and approved the final manuscript.

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Figure legend

Figure 1: Flow chart of the study.

Figure 2: Adjusted probabilities (and 95%-confidence intervals) of being in the upper tertile of the cardiovascular risk score as a function of the number of negative lifestyle factors.

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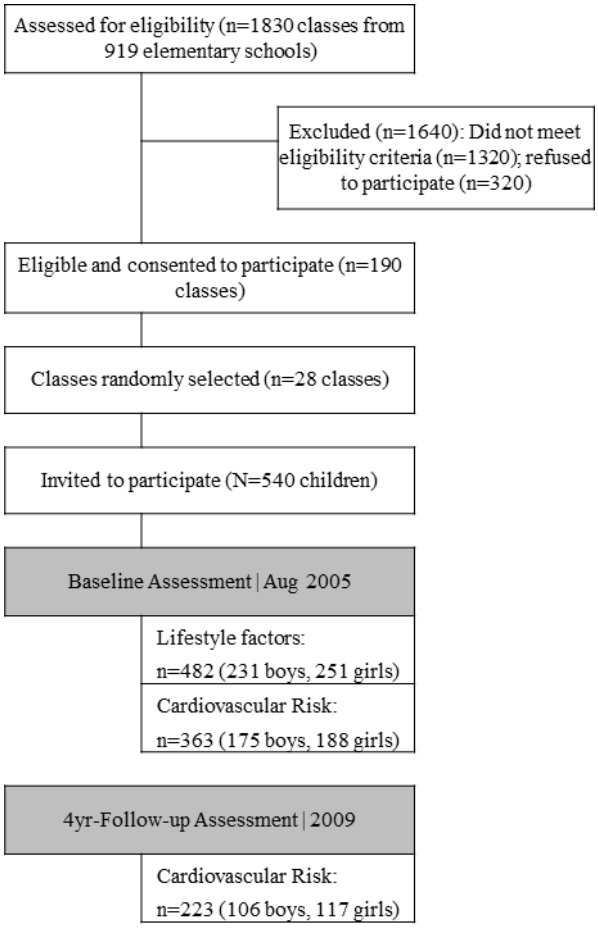

Figure 2: Adjusted probabilities (and 95%-confidence intervals) of being in the upper tertile of the cardiovascular risk score as a function of the number of negative lifestyle factors.